

CLAIMS

We claim:

1. An isolated human antibody or antigen-binding portion thereof that specifically binds to HIV-1 gp120 protein and that has HIV-1 neutralizing activity, wherein said antibody or antigen-binding portion thereof recognizes an epitope on a V1/V2 domain of HIV-1 gp120, wherein said epitope is dependent on the presence of a sequence in the V1 loop.
2. The isolated human antibody or antigen-binding portion thereof according to claim 1, wherein said antibody or antigen binding portion thereof recognizes an epitope on a V1 domain of HIV-1 gp120.
3. The isolated human antibody or antigen-binding portion thereof according to claim 1, wherein said antibody or antigen binding portion thereof recognizes a linear epitope on a V1 domain of HIV-1 gp120.
4. The isolated human antibody or antigen-binding portion thereof according to claim 1, wherein said antibody or antigen-binding portion thereof does not bind the V1/V2 domain of the gp120 of HIV-1 strain Case-A2.

5. The isolated human antibody or antigen-binding portion thereof according to claim 2, wherein said antibody or antigen-binding portion thereof does not bind the V1/V2 domain of the gp120 of HIV-1 strain Case-A2.

6. The isolated human antibody or antigen-binding portion thereof according to claim 3, wherein said antibody or antigen-binding portion thereof does not bind the V1/V2 domain of the gp120 of HIV-1 strain Case-A2.

7. The isolated human antibody or antigen-binding portion thereof according to claim 1, wherein said antibody or antigen-binding portion thereof does not bind an HIV-1 strain Case-A2 gp120 V1/V2 domain specific epitope.

8. The isolated human antibody or antigen-binding portion thereof according to claim 2, wherein said antibody or antigen-binding portion thereof does not bind an HIV-1 strain Case-A2 gp120 V1/V2 domain specific epitope.

9. The isolated human antibody or antigen-binding portion thereof according to claim 3, wherein said antibody or antigen-binding portion thereof does not bind an HIV-1 strain Case-A2 gp120 V1/V2 domain specific epitope.

10. The isolated human antibody or antigen-binding portion thereof according to any one of claims 1-9, wherein said antibody or antigen binding portion thereof has HIV-1_{gP162} neutralizing activity.

5 11. The isolated human antibody or antigen-binding portion thereof according to any one of claims 1-9, wherein said antibody or antigen binding portion thereof recognizes a linear epitope on a V1 domain of HIV-1_{gP162} gp120.

10 12. The isolated human antibody or antigen-binding portion thereof according to claim 10, wherein said antibody or antigen binding portion thereof recognizes a linear epitope on a V1 domain of HIV-1_{gP162} gp120.

15 13. The isolated human antibody or antigen-binding portion thereof according to claim 1, wherein said antibody binds to a peptide consisting of SEQ ID NO: 3.

20 14. The isolated human antibody or antigen-binding portion thereof according to claim 13, wherein said antibody does not bind to a peptide consisting of SEQ ID NO: 2.

 15. The isolated human antibody or antigen-binding portion thereof according to claim 10,

wherein said HIV-1_{gF162} neutralizing activity is approximately as strong as the HIV-1_{gF162} neutralizing activity of human monoclonal antibody selected from the group consisting of 45D1/B7, secreted by a hybridoma
5 designated by ATCC Accession Number PTA-3002, 58E1/B3, secreted by a hybridoma designated by ATCC Accession Number PTA-3003 and 64B9/A6, secreted by a hybridoma designated by ATCC Accession Number PTA-3004.

16. The isolated human antibody or antigen-binding
10 portion thereof according to any one of claims 1-9 or 12-15, wherein the human antibody is a human monoclonal antibody.

17. The isolated human antibody or
antigen-binding portion thereof according to claim 10
15 wherein the human antibody is a human monoclonal antibody.

18. The isolated human antibody or
antigen-binding portion thereof according to claim 11
wherein the human antibody is a human monoclonal
20 antibody.

19. A hybridoma cell line selected from the group consisting of: cell line 35D10/D2 (ATCC Accession Number PTA-3001), cell line 40H2/C7 (ATCC Accession Number PTA-3006), cell line 43A3/E4 (ATCC Accession

Number PTA-3005), cell line 43C7/B9 (ATCC Accession
Number PTA-3007), cell line 45D1/B7 (ATCC Accession
Number PTA-3002), cell line 46E3/E6 (ATCC Accession
Number PTA-3008), cell line 58E1/B3 (ATCC Accession
5 Number PTA-3003) and cell line 64B9/A6 (ATCC Accession
Number PTA-3004).

20. The human monoclonal antibody produced by a
hybridoma cell line according to claim 19, or an
antigen-binding portion thereof.

10 21. The isolated human antibody or
antigen-binding portion thereof according to claim 1,
wherein said human antibody comprises a heavy chain and
a light chain of the antibody according to claim 20.

22. The isolated human antibody or
15 antigen-binding portion thereof according to claim 1,
wherein said human antibody comprises a heavy chain
CDR1, CDR2 and CDR3 from the antibody according to
claim 20.

23. The isolated human antibody or
20 antigen-binding portion thereof according to claim 1,
wherein said human antibody comprises a heavy chain of
a human antibody according to claim 20.

24. A nucleic acid molecule comprising a nucleotide sequence that encodes the heavy chain of the antibody according to claim 20.

25. A nucleic acid molecule comprising a
5 nucleotide sequence that encodes the light chain of the antibody according to claim 20.

26. The nucleic acid according to claim 24 or claim 25, operably linked to an expression control sequence.

10 27. A host cell transformed with a nucleic acid according to claim 24.

28. The host cell according to claim 27, further transformed with a nucleic acid molecule according to claim 25.

15 29. A method for producing a human antibody according to claim 20, comprising the step of culturing a host cell according to claim 28 and recovering said antibody.

30. A human antibody produced by the method
20 according to claim 29.

31. An isolated human antibody or antigen-binding portion thereof that specifically binds to HIV-1 gp120 protein and that has HIV-1 neutralizing activity, wherein said antibody or antigen-binding portion
5 thereof recognizes an epitope on a V1/V2 domain of HIV-1 gp120, wherein said antibody or antigen binding portion thereof recognizes a linear epitope on a V2 domain of HIV-1 gp120.

32. The isolated human antibody or
10 antigen-binding portion thereof according to claim 31, wherein said antibody or antigen-binding portion thereof recognizes a linear epitope on a V2 domain of HIV-1_{SF162} gp120.

33. The isolated human antibody or
15 antigen-binding portion thereof according to claim 31, wherein said antibody or antigen binding portion thereof has HIV-1_{SF162} neutralizing activity.

34. The isolated human antibody or
antigen-binding portion thereof according to claim 31,
20 wherein said antibody or antigen binding portion thereof recognizes a linear epitope on a V2 domain of HIV-1_{SF162} gp120 and wherein said antibody or antigen binding portion thereof has HIV-1_{SF162} neutralizing activity.

35. The isolated human antibody or antigen-binding portion thereof according to any one of claims 31-34, wherein the human antibody is a human monoclonal antibody.

5 36. The isolated human antibody or antigen-binding portion thereof according to claim 31, wherein said human antibody binds to at least three CCR5 Clade B HIV-1 gp120 proteins.

37. The isolated human antibody or
10 antigen-binding portion thereof according to claim 31, wherein said human antibody binds to a peptide consisting of the sequence of SEQ ID NO: 4.

38. The isolated human antibody or antigen-binding portion thereof according to any one of
15 claims 31-34, wherein said human antibody, wherein said antibody does not bind to a gp120 of HIV-1 IIIB, HBX2, HBX2d or BH10.

39. A hybridoma cell line designated 8.22.2 and having ATCC Accession Number _____.

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40. A human antibody produced by the hybridoma cell line according to claim 39, or antigen-binding portion thereof.

41. The isolated human antibody or antigen-binding portion thereof according to claim 31, wherein said antibody or antigen-binding portion thereof competes with the antibody according to claim 5 40 for binding to an antigen bound by the antibody according to claim 40.

42. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 31, wherein said human monoclonal antibody comprises a 10 heavy chain and a light of the antibody according to claim 40.

43. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 31, wherein said human monoclonal antibody comprises a 15 heavy chain of the antibody according to claim 40.

44. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 31, wherein said human antibody comprises a heavy chain CDR1, CDR2 and CDR3 from the antibody according to 20 claim 40.

45. A nucleic acid molecule comprising a nucleotide sequence that encodes the heavy chain of the antibody according to claim 40.

46. A nucleic acid molecule comprising a nucleotide sequence that encodes the light chain of the antibody according to claim 40.

47. The nucleic acid according to claim 45 or
5 claim 46, operably linked to an expression control sequence.

48. A host cell transformed with a nucleic acid according to claim 45.

49. The host cell according to claim 48, further
10 transformed with a nucleic acid molecule according to claim 46.

50. A method for producing a human antibody according to claim 40 comprising the step of culturing a host cell according to claim 49 and recovering said
15 antibody.

51. A human antibody produced by the method according to claim 50.

52. The isolated human antibody or antigen-binding portion thereof according any one of
20 claims 1 or 31, wherein the antibody or portion thereof has HIV-1 neutralizing activity in vivo.

53. The isolated human antibody or antigen-binding portion thereof according to any one of claims 1 or 31, wherein said antibody has neutralizing activity for more than one primary isolate of HIV-1.

5 54. The isolated human antibody or antigen-binding portion thereof according to claim 53, wherein said antibody has neutralizing activity for more than one primary isolate of HIV-1 in vivo.

55. The isolated human antibody or
10 antigen-binding portion thereof according to any of claims 53, wherein said more than one primary isolate of HIV-1 are members of more than one clade.

56. An isolated human monoclonal antibody or antigen-binding portion thereof that specifically binds
15 to an epitope on a V3 region of HIV-1 gp120, wherein said antibody binds to an epitope on the V3 region of HIV-1, and wherein said antibody does not specifically bind to a peptide consisting of SEQ ID NO: 9.

57. The isolated human monoclonal antibody or
20 antigen-binding portion thereof according to claim 56, wherein said V3 region is the V3 region of HIV-1_{SF162} gp120.

58. A hybridoma cell line selected from the group consisting of: cell line 8.27.3 (ATCC Accession Number

PTA-3009) and cell line 8E11/A8 (ATCC Accession Number _____).

59. The human antibody, produced by a hybridoma cell line according to claim 58, or antigen-binding
5 portion thereof.

60. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 56, wherein said antibody comprises a heavy chain and a light chain of a human antibody according to claim 59.

10 61. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 56, wherein said human antibody comprises a heavy chain CDR1, CDR2 and CDR3 from the antibody according to claim 59.

15 62. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 56, wherein said antibody comprises a heavy chain of a human antibody according to claim 59.

20 63. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 56, wherein said antibody or antigen-binding portion thereof competes with a human antibody according to claim 59 for binding to an antigen bound by said antibody according to claim 59.

64. The isolated human monoclonal antibody or antigen-binding portion thereof according to any one of claims 56, 57 or 59-63, wherein said antibody has HIV-1 neutralizing activity.

5 65. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 64, wherein said antibody has HIV-1_{SF162} neutralizing activity.

10 66. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 64, wherein the antibody or portion thereof has HIV-1 neutralizing activity in vivo.

15 67. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 64, wherein said antibody has neutralizing activity for more than one primary isolate of HIV-1.

20 68. The isolated human antibody or antigen-binding portion thereof according to claim 67, wherein said for more than one primary isolate of HIV-1 are members of more than one clade.

69. The isolated human antibody or antigen-binding portion thereof according to any one of claims 1, 31 or 56, wherein said antibody or portion

thereof inhibits the binding of HIV-1 gp120 to human CXCR4 receptor.

70. The isolated human antibody or antigen-binding portion thereof according to any one of
5 claims 1, 31 or 56, wherein said antibody or portion thereof inhibits the binding of HIV-1 gp120 to human CCR5 receptor.

71. A nucleic acid molecule comprising a nucleotide sequence that encodes the heavy chain of the
10 antibody according to claim 59.

72. A nucleic acid molecule comprising a nucleotide sequence that encodes the light chain of the antibody according to claim 59.

73. The nucleic acid according to claim 71 or
15 claim 72, operably linked to an expression control sequence.

74. A host cell transformed with a nucleic acid according to claim 71.

75. The host cell according to claim 74, further
20 transformed with a nucleic acid molecule according to claim 72.

76. A method for producing a human antibody according to any one of claim 59 comprising the step of culturing a host cell according to claim 75 and recovering said antibody.

5 77. A human antibody produced by the method according to claim 76.

78. The isolated human monoclonal antibody or antigen-binding portion thereof according any one of claims 17-18 or 56, wherein the antibody or portion
10 thereof is an immunoglobulin G (IgG), an IgM, an IgE, an IgA or an IgD molecule, or is derived therefrom.

79. The isolated human monoclonal antibody or antigen-binding portion thereof according claim 16, wherein the antibody or portion thereof is an
15 immunoglobulin G (IgG), an IgM, an IgE, an IgA or an IgD molecule, or is derived therefrom.

80. The isolated human monoclonal antibody or antigen-binding portion thereof according claim 35, wherein the antibody or portion thereof is an
20 immunoglobulin G (IgG), an IgM, an IgE, an IgA or an IgD molecule, or is derived therefrom.

81. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 78, wherein the antibody or portion thereof is an IgG or is derived therefrom.

5 82. The isolated human monoclonal antibody or antigen-binding portion thereof according to any one of claims 79-80, wherein the antibody or portion thereof is an IgG or is derived therefrom.

83. The isolated human monoclonal antibody or
10 antigen-binding portion thereof according to claim 81, wherein the IgG is selected from an IgG1, an IgG2, an IgG3 or an IgG4 subtype.

84. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 82,
15 wherein the IgG is selected from an IgG1, an IgG2, an IgG3 or an IgG4 subtype.

85. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 16, wherein the antibody or portion thereof is labeled.

20 86. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 35, wherein the antibody or portion thereof is labeled.

87. The isolated human monoclonal antibody or antigen-binding portion thereof according to any one of claims 17-18 or 56, wherein the antibody or portion thereof is labeled.

5 88. The isolated human monoclonal antibody or antigen-binding portion thereof according to any one of claims 85-86, wherein the label is selected from the group consisting of a radiolabel, an enzyme label, a toxin and a magnetic agent.

10 89. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 87, wherein the label is selected from the group consisting of a radiolabel, an enzyme label, a toxin and a magnetic agent.

15 90. The isolated antigen-binding portion thereof according to any one of claims 1, 31 or 56, wherein said antigen-binding fragment is an Fab fragment, an F(ab')₂ fragment or an F_v fragment.

20 91. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 16, wherein the antibody is a single chain antibody.

92. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 35, wherein the antibody is a single chain antibody.

93. The isolated human monoclonal antibody or antigen-binding portion thereof according to any one of claims 17-18 or 56, wherein the antibody is a single chain antibody.

5 94. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 16, wherein the antibody is a chimeric antibody.

95. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 18,
10 wherein the antibody is a chimeric antibody.

96. The isolated human monoclonal antibody or antigen-binding portion thereof according to any one of claims 17-18 or 56, wherein the antibody is a chimeric antibody.

15 97. The chimeric antibody according to claim 96, wherein the chimeric antibody comprises framework regions and CDR regions from different human monoclonal antibodies.

98. The chimeric antibody according to any one of
20 claims 94-95, wherein the chimeric antibody comprises framework regions and CDR regions from different human monoclonal antibodies.

99. The chimeric antibody according to claim 96, wherein the chimeric antibody comprises framework regions from a first human monoclonal antibody and CDR regions from a second human monoclonal antibody.

5 100. The chimeric antibody according to any one of claims 94-95, wherein the chimeric antibody comprises framework regions from a first human monoclonal antibody and CDR regions from a second human monoclonal antibody.

10 101. The chimeric antibody according to claim 96, wherein the chimeric antibody comprises CDR regions from at least two different human monoclonal antibodies.

15 102. The chimeric antibody according to claim 96, wherein the chimeric antibody is bispecific.

103. The chimeric antibody according to any one of claims 94-95, wherein the chimeric antibody is bispecific.

20 104. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 16 wherein the antibody or portion thereof is derivatized.

105. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 35 wherein the antibody or portion thereof is derivatized.

106. The isolated human monoclonal antibody or
5 antigen-binding portion thereof according to any one of claims 17-18 or 56, wherein the antibody or portion thereof is derivatized.

107. The isolated human monoclonal antibody or antigen-binding portion thereof according to claim 106,
10 wherein the antibody or portion thereof is derivatized with polyethylene glycol, at least one methyl or ethyl group or at least one carbohydrate moiety.

108. The isolated human monoclonal antibody or antigen-binding portion thereof according to any one of
15 claims 103-104, wherein the antibody or portion thereof is derivatized with polyethylene glycol, at least one methyl or ethyl group or at least one carbohydrate moiety.

109. A composition comprising the antibody or
20 portion thereof according to any one of claims 1-18, 20-23, 30-38, 40-44, 51-57, 59-70 or 77 and a pharmaceutically acceptable carrier.

110. The composition according to claim 109 further comprising at least one additional therapeutic agents.

111. The composition according to claim 110,
5 wherein said one or more additional therapeutic agents are selected from the group consisting of: anti-viral agents, immunomodulators and immunostimulators.

112. A kit comprising a container comprising the antibody or portion thereof according to any one of
10 claims 1-18, 20-23, 30-38, 40-44, 51-57, 59-70 or 77, and a pharmaceutically acceptable carrier therefor.

113. The kit according to claim 112, further comprising instructions for use.

114. The kit according to any one of claims 112-
15 113, further comprising another anti-viral agent, an immunomodulator or an immunostimulator, or any combination thereof.

115. A method for treating a subject with an HIV-1 infection comprising the step of administering an
20 antibody according to any one of claims 1-18, 20-23, 30-38, 40-44, 51-57, 59-70 or 77, or an antigen-binding portion thereof.

116. A method for preventing or inhibiting HIV-1 infection in a subject comprising the step of administering an antibody according to any one of claims 1-18, 20-23, 30-38, 40-44, 51-57, 59-70 or 77,
5 or an antigen-binding portion thereof.

117. A method for preventing or lessening the severity of a condition caused by HIV-1 infection in a subject comprising the step of administering an antibody according to any one of claims 1-18, 20-23,
10 30-38, 40-44, 51-57, 59-70 or 77, or an antigen-binding portion thereof.

118. A method for inhibiting HIV-1 virus binding to a T cell comprising the step of contacting said virus with an antibody according to any one of claims
15 1-18, 20-23, 30-38, 40-44, 51-57, 59-70 or 77, or an antigen-binding portion thereof.

119. A method for inhibiting HIV-1 virus infection of a T cell comprising the step of contacting said virus with an antibody according to any one of claims
20 1-18, 20-23, 30-38, 40-44, 51-57, 59-70 or 77, or an antigen-binding portion thereof.

120. A method of inhibiting HIV-1 gp120-mediated binding comprising the step of contacting a gp120-expressing HIV-1 virus with an antibody according to

any one of claims 1-18, 20-23, 30-38, 40-44, 51-57, 59-70 or 77, or an antigen-binding portion thereof.

121. The method according to any one of claims 115-120, further comprising the step of administering
5 one or more additional therapeutic agents.

122. The method according to claim 121, wherein said one or more therapeutic agents are selected from the group consisting of: anti-viral agents, immunomodulators and immunostimulators.

10 123. The method according to any one of claims 115-117 or 121, wherein said administering step is performed via an intravenous, subcutaneous, intramuscular, oral, pulmonary inhalation, transdermal or parenteral route.

15 124. The method according to any one of claims 115-120, wherein said antibody or antigen-binding portion thereof is labeled or is part of a fusion protein.

20 125. The method according to claim 124, wherein said antibody or antigen-binding portion is labeled with a radiolabel, is joined to an immunotoxin or a toxin.

126. The method according to claim 124 wherein said fusion protein comprises a toxic peptide.

127. A method for producing a human antibody that specifically binds HIV-1 gp 120, comprising the steps
5 of:

- a) immunizing a non-human mammal at least some of whose B cells are capable of producing human immunoglobulin heavy chains and human immunoglobulin light chains with and HIV-1
10 gp120 antigen; and
- b) recovering said human antibody that specifically binds HIV-1 gp120 from said non-human mammal.

128. The method according to claim 127 , wherein
15 said gp 120 antigen is selected from the group consisting of: recombinant gp120, gp120 peptides, gp120 polypeptides, a fusion protein comprising a recombinant gp120, a fusion protein comprising a gp120 peptide and a fusion protein comprising a gp120 polypeptide.

20 129. The method according to claim 127, further comprising the steps of:

- a) isolating a cell that produces said human antibody that specifically binds HIV-1 gp120 from said non-human mammal;
- 25 b) immortalizing said human antibody-producing cell; and

- c) recovering said human antibody that specifically binds HIV-1 gp120 from the immortalized cell.

130. The method according to claim 127, further
5 comprising the steps of:

- a) isolating a cell that produces said human antibody that specifically binds HIV-1 gp120 from said non-human mammal;
- 10 b) isolating the genes encoding said antibody from the isolated cell;
- c) introducing said genes isolated in step b) into a host cell; and
- 15 d) recovering said human antibody that specifically binds HIV-1 gp120 from said host cell.

131. The method according to any one of claims 127-130, wherein said non-human mammal is a mouse.

132. The method according to any one of claims 127-130, wherein said non-human mammal is a XENOMOUSE®
20 mouse.

133. A method for identifying a region of HIV-1 gp120 for use as an HIV-1 vaccine comprising the steps of:

- a) producing in a non-human mammal a human monoclonal antibody and isolating said human monoclonal antibody that binds gp120 and that has neutralizing activity for HIV-1; and
- 5 b) identifying an epitope on said gp120 that is bound by said antibody.

134. The method according to claim 133, wherein the human antibody is a monoclonal antibody.

135. An isolated cell line that produces the
10 antibody according to any one of claims 1-18, 20-23, 30-38, 40-44, 51-57, 59-70 or 77.

136. The cell line according to claim 135 that is a hybridoma.

137. The hybridoma according to claim 136 that
15 produces an antibody selected from the group consisting of 35D10/D2, secreted by a hybridoma designated by ATCC Accession Number PTA-3001, 40H2/C7, secreted by a hybridoma designated by ATCC Accession Number PTA-3006, 43A3/E4, secreted by a hybridoma designated by ATCC
20 Accession Number PTA-3005, 43C7/B9, secreted by a hybridoma designated by ATCC Accession Number PTA-3007, 45D1/B7, secreted by a hybridoma designated by ATCC Accession Number PTA-3002, 46E3/E6, secreted by a hybridoma designated by ATCC Accession Number PTA-3008,
25 58E1/B3 secreted by a hybridoma designated by ATCC

Accession Number PTA-3003, 64B9/A6, secreted by a
hybridoma designated by ATCC Accession Number PTA-3004,
8E11/A8 secreted by a hybridoma designated by ATCC
Accession Number _____, 8.27.3, secreted by a
5 hybridoma designated by ATCC Accession Number PTA-3009
and 8.22.2, secreted by a hybridoma designated by ATCC
Accession Number _____.

138. A non-human mammal expressing a human
antibody that specifically binds HIV-1 gp120.

- 10 139. A human antibody according to claim 1 that
competes with an antibody according to claim 20 for
binding to an antigen bound by an antibody according to
claim 20.